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Changes in the Trend of Sexually Acquired Chlamydia Infections in Sweden and the Role of Testing: A Time Series Analysis

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Background: We investigated the notification trends of sexually acquired chlamydia (chlamydia) and its association with testing in Sweden before (1992–2004) and after (2009–2018) the discovery of a new variant of *Chlamydia trachomatis* (nvCT).

Methods: We applied monthly time series analysis to study chlamydia trends and annual time series to study chlamydia rates adjusted for testing. We analyzed incidence nationally and by county group (based on able and unable to detect nvCT at time of discovery).

Results: We present data on 606,000 cases of chlamydia and 9.9 million persons tested. We found a U-shaped chlamydia trend during the period 1992–2004, with an overall increase of 83.7% from 1996 onward. The period 2009–2018 began with a stable trend at a high incidence level followed by a decrease of 19.7% during the period 2015–2018. Peaks were seen in autumn and through during winter and summer. Similar results were observed by groups of county, although with varying levels of increase and decrease in both periods. Furthermore, increased testing volume was associated with increased chlamydia rates during the first period ($P = 0.019$) but not the second period.

Conclusions: Our results showed that chlamydia trends during the period 2009–2018 were not driven by testing, as they were during the period 1992–2004. This suggests less biased notified chlamydia rates and thus possibly a true decrease in chlamydia incidence rates. It is important to adjust case rates for testing intensity, and future research should target other potential factors influencing chlamydia rates.

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This work was supported by the Public Health Agency of Sweden.

Conflict of Interest and Sources of Funding: None declared.

Ethics Approval: Regional Ethics Review Board in Stockholm (reference number: 2012/1710-31/3).

Data Sharing Statement: No additional data are available.

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Received for publication June 20, 2020, and accepted October 9, 2020.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (http://www.stdjournal.com).

DOI: 10.1097/OLQ.0000000000001318

Genital chlamydial infection (chlamydia) is the most frequently reported bacterial sexually transmitted infection in Sweden and is highly prevalent globally.[1,2] Because most chlamydia infections are asymptomatic and can cause reproductive sequelae in both men and women,[3,4] the goal of the chlamydia control program in Sweden is to identify and treat cases of chlamydia to reduce both the burden of infection and sequelae of chlamydia in the population.

The control program in Sweden is implemented through a universal surveillance system for cases of chlamydia, with generous opportunistic testing, treatment, and partner notification at no cost to the individual. Chlamydia became notifiable in Sweden in 1988, and chlamydia notification rates and number of persons tested doubled between 1997 and 2018.[5] Opportunistic screening executed in Sweden has varying testing uptake and characteristics of tested persons in time and place,[6] and the effectiveness of this intervention has been questioned previously.[7,8]

In 2006, a new genetic variant of *Chlamydia trachomatis* (nvCT; new Swedish variant of *C. trachomatis*) was discovered in Sweden.[9] Up to that time, two-thirds of the tests in Sweden were analyzed by nucleic acid amplification tests, which could not detect nvCT.[9,10] This unforeseen incident led to false-negative test results,[11] leading to many thousands of undetected cases of chlamydia and missed partner notification, even before 2006.[12,13] After the introduction of assays able to detect nvCT in all counties, the national notification rates of chlamydia increased in 2007 to 2008 owing to the detection of accumulated undiagnosed cases of nvCT.[14] Meanwhile, only sporadic or no cases of nvCT were reported in a number of European countries and the United States.[15–20]

After the emergence of nvCT in Sweden, control measures such as testing for chlamydia and partner notification were intensified on a national level. This constitutes a natural experiment, where we can study chlamydia trends under 2 different control regimes, one historical pre-nvCT and one intensified post-nvCT. Thus, we had 2 objectives in this study: first, we wished to describe and compare monthly time series of chlamydia before and after the discovery of nvCT in Sweden, both nationally and comparing counties able to detect nvCT before 2006 with those unable to, and second, we wished to relate annual chlamydia rates to testing intensity, as this would assist us in interpreting chlamydia notification rates.

METHODS AND MATERIALS

Data

Cases of chlamydia were retrieved from the national register of mandatory reportable infectious diseases (SmiNet-2) at the Public Health Agency of Sweden.[21] Reporting of laboratory-confirmed cases of chlamydia from any body site (urogenital, pharyngeal, and anal samples) in Sweden is mandatory, universal, and anonymized and includes notification from the laboratory and clinician. There were 95% to 97% of reported chlamydia cases

that were acquired via sexual contact, with most of the remaining cases having no information on the route of transmission and very few cases acquired via vertical transmission (0.05%–0.1%).[5] Enzyme-linked immunosorbent assays and culture were used before 1996, when nucleic acid amplification tests were gradually introduced.

We classified counties (n = 21) into 2 groups based on their ability to detect nvCT before 2006[9,10]: group "able-to-detect" (n = 8) and group "unable-to-detect" (n = 13; Table S1, http://links.lww.com/OLQ/A570). We carried out the analyses for 2 periods: 1992–2004 (before nvCT) and 2009–2018 (after nvCT). We excluded data for the period 2005–2008 (Fig. 1): 2005–2006 because of potentially missed cases of nvCT and 2007–2008 because of a spurious incidence peak and a subsequent decrease caused by catch-up of nvCT.

For the monthly analysis (first objective), we aggregated cases of chlamydia by 4-week periods (here called a "month"), resulting in 13 months of equal length per year (also called the Equal Month calendar), except for extra days in week 53 in some years, which were added to the last week of month 13.[22] Midyear population counts were obtained from Statistics Sweden by year and county.[23]

For the yearly analysis (second objective), we used population-based reported annual number of persons tested for chlamydia collected at the Public Health Agency of Sweden from the microbiological laboratories in charge of chlamydia testing in each county, which serve all health care facilities (private and public). For the period 2009–2018, on average, 23.4% of counties reported the number of tests performed instead, which could include multiple tests done on the same person at the same testing event (data not available for the first period). Because the reported testing data were in aggregated format, it was not possible to eliminate potential recount, and we chose to interpret and refer to both types of data as number of persons tested in our analyses. We defined the proportion of persons tested as the number of persons tested (including tests performed) per population aged 15 to 64 years in each county, being the age interval where most tests are performed. Cases of chlamydia and proportions of tests per population were aggregated nationally and by county group (Table S1, http://links.lww.com/OLQ/A570).

Statistical Analyses

Monthly Chlamydia Time Series Analysis (First Objective)

We applied time series analysis[24] to investigate whether chlamydia incidence differed: (1) between periods at the national level and (2) between groups of counties, both within and between periods. Time series for incidence rates (IRs) were fit as negative binomial regression models for chlamydia notification counts with corresponding population counts as the denominator. Models included an overall nonlinear trend, overlaid with monthly effects to capture seasonal variations in incidence, and were adjusted for autocorrelation, that is, the correlation between number of cases from month to month (Equation 1S, http://links.lww.com/OLQ/A570). Trends were modeled as restricted cubic spline functions with 3 to 5 knots (including boundary knots), corresponding to splitting the observed time ranges into 2 to 4 intervals of equal length. Seasonality was modeled via fixed monthly effects averaging to zero over a full year. Models were fit via maximum likelihood. The numbers of parameters for spline terms and autocorrelation terms were increased until the final model did not improve according to the Akaike information criterion or a likelihood ratio test at a significance level of 0.05.

We expressed the trend as monthly IRs (notified cases per 100,000 population) and seasonality as incidence rate ratios, calculated as the ratio of each monthly IR relative to the average annual chlamydia IR for the corresponding year. We reported 95% Wald confidence intervals (CIs) for all components.

Models were fitted separately for each period at the national level and each group of counties. We compared within and between periods via contrasts of the corresponding model parameters, tested with Wald tests at a significance level of 0.05. Equality of model components involving more than 1 parameter (spline and seasonality parameters) was tested using multivariate Wald tests with appropriate degrees of freedom.

Yearly Chlamydia Time Series Analysis With Testing (Second Objective)

We fitted the negative binomial regression models for the annual chlamydia IRs (notified chlamydia cases per 100,000 population), with population as an offset and adjusted for individual counties as fixed effects. The model included the proportion of

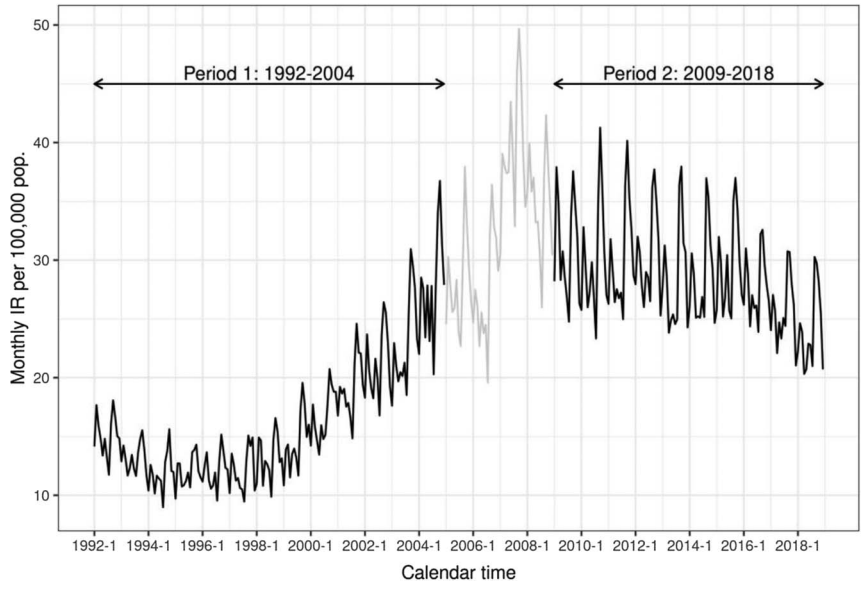

Figure 1. Reported monthly national incidence rates of chlamydia cases per 100,000 population in Sweden, 1992 to 2018. Excluded years (2005–2008) are highlighted with gray color.

tested individuals at the county level, a linear and quadratic yearly trend, and a linear interaction term between the proportion tested and year (Equation 2S, http://links.lww.com/OLQ/A570). The final model was selected based on improving the Akaike information criterion value and likelihood ratio test at a significance level of 0.05. We present model parameters as IRs with 95% CIs to visualize trends over time.

We performed all statistical analyses using STATA version 15[25] and used R statistical software[26] to produce graphs.

RESULTS

Monthly National Chlamydia Time Series

We included 605,889 cases of chlamydia in the analysis (Fig. 1S, http://links.lww.com/OLQ/A570), with 361,330 (60%) cases reported during the period 2009–2018 (Fig. 1) and overall 58% in women and 85% in 15- to 29-year-olds.

We found the trend to follow a U-shape during the period 1992–2004 (Table S2, http://links.lww.com/OLQ/A570; Fig. 2A): incidence declined from the start of the period, reaching the lowest IR in 1996, followed by a subsequent gradual increase with the highest IR toward the end of 2004, an increase of 83.7% from 1996. The second period (2009–2018) was characterized by an initially stable, then slightly decreasing trend from 2015 onward (Fig. 2B); at the beginning of the period, IRs were higher than the levels at the end of the first period. Overall, the rates decreased by 19.7% from 2009 to 2018. The trends were statistically significantly different between the 2 periods ($P < 0.001$).

Although seasonality was also statistically significantly different between periods ($P < 0.001$), the national within-year seasonality was similar, with the highest IR compared with the annual average chlamydia IR in months 9 to 11 (autumn) and the lowest IR in month 8 (summer) and month 1 (mid-winter), with the autumn peak slightly shifted in the second period (Table S3, http://links.lww.com/OLQ/A570; Fig. 2S, http://links.lww.com/OLQ/A570).

Monthly Chlamydia Time Series by Group of Counties

Trends by groups of counties followed the same shape as the whole country during both periods (Tables S4, S5, http://links.lww.com/OLQ/A570). Chlamydia IR was higher in unable-to-detect counties from 1992 to 2001. After 1996, however, the trend in unable-to-detect counties increased at a slower rate (by 75%) than in the able-to-detect counties (by 159%; Fig. 2C). The trends were statistically significantly different between groups of counties ($P < 0.001$) within this period. Throughout the second period, the estimated IR in the unable-to-detect group was higher compared with the able-to-detect group (Fig. 2D). From 2009 to 2018, decreases of 11.6% in the able-to-detect and of 23.5% in the unable-to-detect group were seen with almost convergence toward the end of 2018.

Seasonality patterns were the same as for the national model (Tables S6, S7, http://links.lww.com/OLQ/A570), with no statistically significant differences found between groups of counties within each period ($P = 0.349$ and $P = 0.450$, respectively).

Yearly Chlamydia Time Series With Testing

We included 9,902,855 persons tested for chlamydia in the analysis (Table S1, http://links.lww.com/OLQ/A570). From 1992 to 2004, between 305,946 and 423,442 persons were tested annually (i.e., between 5.2% and 6.9% of the 15- to 64-year-old population), whereas for the second period, between 471,052 and 591,460 individuals were tested, corresponding to 7.2% to 8.5% per year. During the first period, the proportion of the population tested annually was similar between the able-to-detect (min, 5.0%; max, 7.1%) and unable-to-detect (min, 5.2%; max, 6.8%) groups (Fig. 3). In the second period, the proportion of population tested was slightly higher, with 7.1% to 7.7% and 7.2% to 9.0% in each group, respectively. During the first period, on average, 77% of all tests were performed in women, compared with 68% in the second period (Table S8, http://links.lww.com/OLQ/A570). Limited data on the age groups among tested population during the period 2009–2018 revealed that on average 66% of tested population were in age group 15 to 29 years (Table S9, http://links.lww.com/OLQ/A570).

The model for chlamydia trend adjusted for the proportion of tested population in the first period estimated a statistically significant U-shaped yearly trend. Moreover, an increase in the

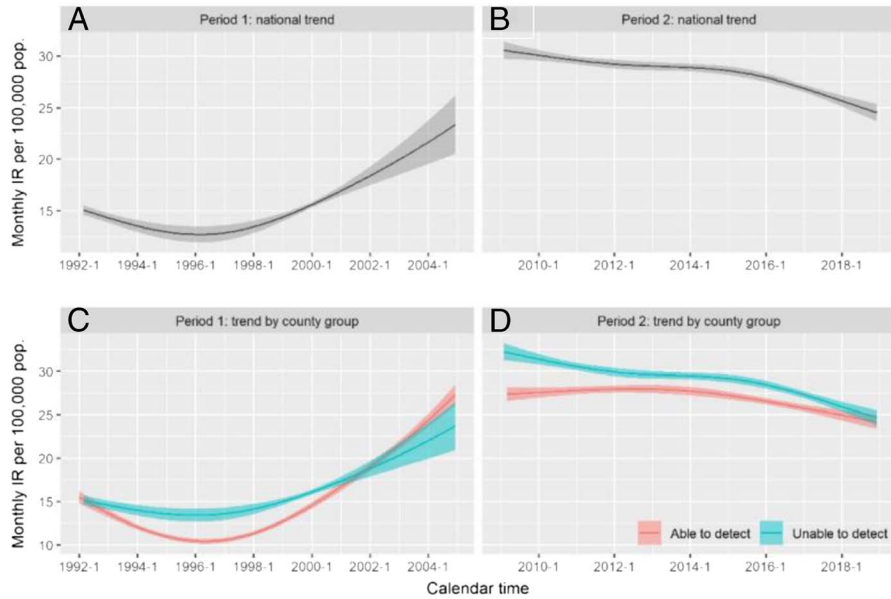

Figure 2. Estimated chlamydia trend (monthly IR per 100,000 population), 1992 to 2004 and 2009 to 2018, for the national chlamydia cases (A and B) and by group of counties (C and D). A and B, Black solid line represents national IRs; shaded area represents 95% CIs. C and D, Black solid line represents able-to-detect counties; black dashed line represents unable-to-detect counties. Shaded area represents 95% CIs.

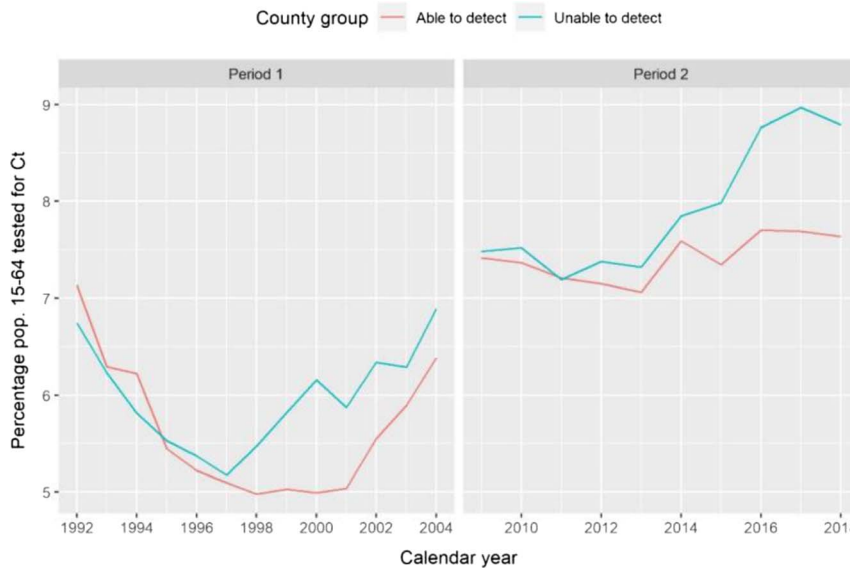

Figure 3. Mean proportion of tested population (age, 15–64 years) for chlamydia, 1992 to 2004 and 2009 to 2018, by group of counties. Black solid line represents able-to-detect counties; black dashed line represents unable-to-detect counties.

proportion of the tested population was significantly associated with an increase in chlamydia IR, but this effect declined slightly, yet statistically significantly, with time (Table S10, http://links.lww.com/OLQ/A570). Moreover, the association between the proportion of tested population and chlamydia IR varied over the first period (interaction term, $P < 0.019$). Thus, for a 1-unit increase (+1%) in the proportion of the population tested, we estimated an expected 7.0% (95% CI, 4.1%–9.5%) increase in annual chlamydia IR in 1992, but the corresponding annual increase in chlamydia IR in 2004 was only 2.3% (95% CI, 0.01%–4.9%).

We estimated a similar significant positive association and a gradual decline of the effect in each county group: in 1992, a 1-unit increase (+1%) in the proportion of the tested population was associated with a 10.2% (95% CI, 4.3%–16.4%) increase in chlamydia IR in able-to-detect counties and 4.8% (95% CI, 2.1%–7.7%) in unable-to-detect counties (Table S10, http://links.lww.com/OLQ/A570). Meanwhile in 2004, we estimated a nonstatistically significant effect (0.01% [95% CI, −0.1% to 5.0%]) in the able-to-detect group, but a statistically significant increase in the unable-to-detect group (3.5% [95% CI, 0.6%–6.5%]; solid lines in Fig. 4). Specifically, the predicted effect of increased testing on estimated IR diminished between 1992 and 2004 (Fig. 4). To visualize this effect, we predicted chlamydia IR from 1992 to 2004 based on the model in Table S8 (http://links.lww.com/OLQ/A570) for a hypothetical annual testing coverage increased by 1% for each year; the predicted counterfactual chlamydia IR was higher throughout (grey lines in Fig. 4), although with a strongly diminishing increase for the able-to-detect group toward 2004.

During the period 2009–2018, we estimated a statistically significant decreasing quadratic annual trend. Notably, we did

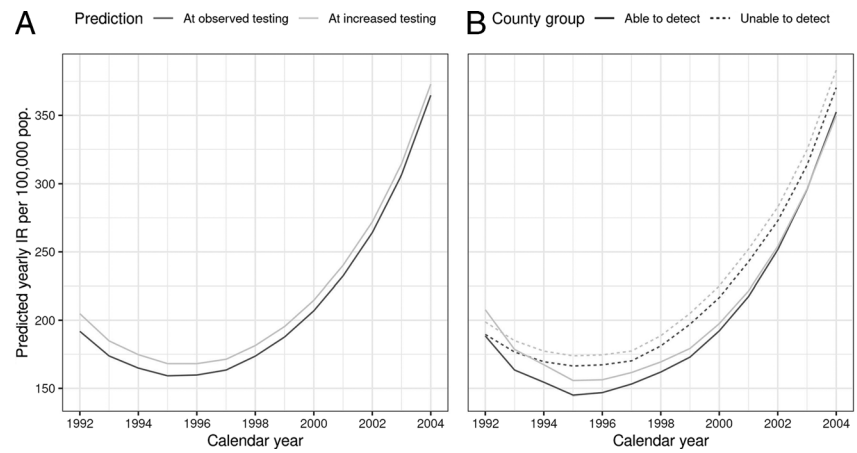

Figure 4. Estimated annual chlamydia IR adjusted for proportion of population tested nationally (A) and by group of counties (B), 1992 to 2004. Solid black line represent estimated IR from the model, grey solid line represent counterfactual IR with 1% increased proportion of tested population (A). Black solid line represents able-to-detect counties estimated IR from the model, grey solid line represent counterfactual IR with 1% increased proportion of tested population in able-to-detect counties (B). Black dashed line represents unable-to-detect counties estimated IR from the model, grey dashed line represent counterfactual IR with 1% increased proportion of tested population in unable-to-detect counties (B).

not find an association between the proportion of the population tested and chlamydia IR, either at the national level or by group of counties (Table S10, http://links.lww.com/OLQ/A570).

DISCUSSION

Our results show a significant change in national chlamydia trends from a U-shaped trend during the period 1992–2004 to the stable and then decreasing trend during the period 2009–2018, which was also consistent in the analysis by group of counties. The seasonality was similar for both periods in all analyses, with the highest rates reported during early autumn. We also found that an increasing proportion of the tested population aged 15 to 64 years was associated with an increase in chlamydia notification rates in the first period both nationally and by group of counties, but not in the second period.

The incident with nvCT in Sweden allowed us to separate 2 periods (before and after the introduction of nvCT) and study chlamydia trends. Estimated chlamydia trends by county groups differed in their magnitude already in the first study period. After the initial decrease, relatively stable trends during the period 1995–1998, an increase since 1998 to 2004 was seen in both types of counties with different pace: the estimated chlamydia trend adjusted for testing in unable-to-detect counties increased at a slower rate compared with able-to-detect counties. This difference in the rate of increase could not be explained by nvCT because it emerged in 1 to 3 counties in 2002 to 2003 and gradually spread to all unable-to-detect counties toward 2006, as was estimated in a modeling study.[13] The biggest long-term role nvCT had was national reinforcement of control measures (testing and following partner notification) in the second period, including adoption of the National action plan for chlamydia prevention.[27] During the period 2009–2018, chlamydia notification rates continued to decline in both groups of counties with the proportion of nvCT among all chlamydia cases dropping to low levels (5%) in the respective group of counties toward 2015.[28] Notably, IRs in both groups of counties started at high levels in 2009 (i.e., the start of the second period), then successively dropped toward the end of 2018, reaching a pre-nvCT level. Thus, nvCT being under control and unable to affect chlamydia trends in the latter period suggests that testing volumes and other factors, which we have not studied (e.g., effectiveness of partner notification), could play a role.

Possible underlying reasons for chlamydia rates being different between 2 groups of counties may lie in the differences in testing volumes,[6] organization of partner notification process: centralized versus decentralized, reaching out for the sexual partners with varying time (6 months and up to 12 months back), and varying success in reaching identified partners of index cases.[29,30,31s] In addition, investments in primary and secondary prevention, strong leadership, and multisectoral collaboration at the regional level were identified as potential successful factors in controlling chlamydia in some counties but not others.[32s]

We assessed the role of testing and found that, in the first study period, an increase in chlamydia rates was associated with an increased proportion of tested population 15 to 64 years of age. Opportunistic screening in Sweden has expanded since the mid-1990s through free-of-charge testing at outpatient clinics and since the early 2000s, with self-sampling at home and sample analysis at the laboratory, with no age limit.[33s,34s] Previous studies reported a strong relationship between increasing testing rates and increasing chlamydia rates,[6,35s–38s] including repeat testing after a previous positive test result.[39s,40s] However, in the second period, we did not find an association between chlamydia IR and testing coverage, although the latter continued to rise. This suggests that estimated chlamydia IR is no longer driven by increased testing volumes in the reached population targeted for testing and suggests that chlamydia IR estimates are less biased in the second compared with the first period. Increasing notified chlamydia rates hand in hand with increasing testing in the first period was likely prone to the biased screening coverage, when likely underestimation of the true trend occurred. Similar influence of time-varying biases on the notified case rates was reported elsewhere.[41s] In contrast, the decline in adjusted chlamydia notification rates in the second period could possibly reflect a true decline in chlamydia IRs. This is also indirectly supported by a reported decline in potential sequelae of chlamydia infection (pelvic inflammatory disease and ectopic pregnancies) in Sweden during the second period.[28] Alternatively, notification rates could still decline, whereas true IRs are not declining because asymptomatic infected people are not reached fully by screening and continue spreading chlamydia infection. Possible change in the characteristics of the tested population (demographics and sexual behavior) might have taken place during the second period, as reported elsewhere.[37s] However, our data on sex distribution and limited data on age groups among the tested population during the period 2009–2018 suggest no such drastic changes occurred: two-thirds of women and the same proportion of individuals aged 15 to 29 years were among the tested population annually. Individuals not reached by testing could still contribute to the spread of chlamydia, as a UK study that reported antibodies for the past chlamydia infection in a third of 16- to 24-year-old individuals never previously tested for chlamydia.[42s]

Findings from our study agree with reports elsewhere on initial decrease in the late 1980s and early 1990s, which is thought to be attributable to HIV prevention campaigns and fear for HIV.[43s–45s] Consistently increasing chlamydia trends were reported in other countries during the mid-1990s and up to 2010 (e.g., North America,[46s, 47s] Australia,[48s] European Union,[49s] and specifically in neighboring Norway,[36s] Denmark,[50s] and Finland[51s]). Possible reasons for the increase of chlamydia rates in the late 1990s and early 2000s elsewhere and in Sweden were the introduction of more sensitive diagnostic methods and possibly an increased chlamydia prevalence in the population,[36s, 50s–52s] as well as a switch to chlamydia high-prevalence target groups for testing,[50s] as suggested previously.[53S] Also, highest chlamydia rates reported during early autumn were consistent with previous results.[54s] The reasons for increased rates in the autumn in Sweden are most likely due to decreased access to testing facilities during summer months (holiday time), as well as the annual national awareness campaign (in place since 2003) on safe sex and testing run in September.[55s] Between 2008 and 2017, the rates of chlamydia remained stable in the European Union and European Economic Area, although rates of chlamydia continued to increase in Denmark, Finland, and Norway, as well as in North America,[1,47s,56s] contrary to what our study found in Sweden.

There are some limitations to our study. First, our analyses are based on notified chlamydia rates and likely underestimate the true IRs of chlamydia, as high proportions of asymptomatic chlamydia infections go undetected,[41s,42s] although our results for the second period suggest that estimated chlamydia IRs are more reliable than for to the first period. Second, reported testing data are a combination of data on persons tested and number of performed tests, which could lead to an overestimation of the proportion of tested population and might consequently affect the relationship between chlamydia rates and proportion of tested population. However, available data on the period 2009–2018 suggest a reasonably stable proportion (almost three-quarters) of counties reporting the number of persons tested. Importantly, the analysis of monthly trends is not affected by this limitation. Lastly, the described chlamydia trends and association with testing, as well as

the suggested explanations for them, may not generalize easily to countries other than Sweden because of differences in health care systems and the range and coverage by control measures. The key strengths of our study is the high-quality surveillance data, collected during a 23-year period, including almost 606,000 cases of chlamydia and nearly 9.9 million tests for chlamydia.[57s] In addition, we were able to stratify time series analysis by group of counties, which has not been previously reported. Our findings were also strengthened by the adjustment of chlamydia rates for testing coverage, as Sweden is among the few countries that collect data on testing.

Our results showed that chlamydia trends during the period 2009–2018 were not driven by testing as they were during the period 1992–2004, which suggests that chlamydia notification rates in the former period were more likely underestimating true chlamydia IR. In the second period, chlamydia notification rates were not affected by testing and more likely reflect a true decrease in chlamydia rates. Thus, other factors could contribute to the declining chlamydia rates during the latter period. Therefore, further research is warranted to assist in interpreting chlamydia trends, such as characterizing the tested population in detail (including sociodemographic and sexual behavior) to monitor whether relevant subgroups at risk are reached. Continuous monitoring and interpretation of testing and chlamydia trends have to be maintained, also in the light of possible emergence of other new variants of *C. trachomatis* as what happened again recently in Finland.[58s]

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For further references, please see "Supplemental References," http://links.lww.com/OLQ/A571.